

## REMARKS

### The Office Action

Claims 30, 33, 34, 36, 43, 44, 47, 51, 53-62, and 64-72 are pending in this application. Claims 33, 54-55, 57, and 59 are objected to under 37 C.F.R. § 1.75; claims 30, 33-34, 36, 43-44, 47, 53-55, 57, 61-62, and 72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description; claims 30, 33-34, 36, 43-44, 47, 53-55, 57, 59, 61-62, and 72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement; claims 51, 64-66, and 68-71 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness; and claims 30, 33-34, 43-44, and 47 are provisionally rejected for obviousness-type double patenting over claims 37, 39-40, and 42-58 of copending application no. 11/220,485. By this reply, Applicants amend claim 51, cancel claims 33, 54, 55, 57, 59, and 64-71, add claims 79-89, and address each of the Examiner's rejections.

### Support for the Amendment

Support for new claims 79-89 is found in pending claim 30 and in prior claims 54, 55, 57, 59, and 64-71. The amendment to claim 51 is made to provide consistency between the claims. No new matter is added by the amendment.

### Objections under 37 C.F.R. § 1.75

Claims 33, 54, 55, 57, and 59 are objected to under 37 C.F.R. § 1.75 as being "of improper dependent form for failing to further limit the subject matter of a previous claim" (Office Action, p. 2). The Examiner suggests rewriting the claims in independent form. Thus,

Applicants have cancelled claim 33 and have rewritten claims 54, 55, 57, and 59 in independent form; the subject matter of claims 54, 55, 57, and 59 is now presented in new independent claims 79-82, respectively. Accordingly, this objection can now be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 51, 64-66, and 68-71 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that “claim 51 recites the limitation ‘said polypeptide region’ in line 1 of the claim...[but that] [t]here is insufficient antecedent basis for this limitation in the claim...Similarly, claims 64-66 and 68-71 recite the limitation ‘said region’ in line 1 of the claims” (Office Action, p. 14). Applicants have amended claim 51 to remove the term “region.” Applicants respectfully submit that the rejection of claim 51 can now be withdrawn. In addition, Applicants have cancelled claims 64-66, and 68-71, and have replaced these claims with new claims 83-89, which do not recite the limitation “said region.” Therefore, Applicants respectfully submit that the rejection of claims 64-66 and 68-71 may be withdrawn as well.

Rejections under 35 U.S.C. § 112, first paragraph

*Written Description*

Claims 30, 33-34, 36, 43-44, 47, 53-55, 57, 59, 61-62, and 72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that the rejected claims

contain[] subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Office Action, p. 3.)

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[T]he specification fails to describe the essential characteristics or elements possessed by a representative number of species for a broad genus of the nucleic acid to be utilized in the method as claimed...For example the instant specification fails to describe which amino acids to be substituted, deleted, or inserted, at which positions and in which combinations, particularly at a carboxyl-terminal region of a mature, native, human apoE, such that an encoded polypeptide having at least 90% sequence identity to SEQ ID NO: 2 but without the amino acid sequence of amino acids 260-299 of SEQ ID NO: 2, still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia. (Office Action, pp. 4-5.)

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[T]he claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. (Office Action, p. 5.)

Applicants respectfully traverse this rejection.

Present independent claims 30 and 79-83 are directed to a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia. The method involves intravascularly administering to the mammal a replication-defective adenoviral vector containing a nucleic acid encoding a secreted polypeptide having the particular sequence defined in present independent claims 79, 81, and 82, which sequence is relative to the sequence set forth in SEQ ID NO: 2 (i.e., the polypeptide sequence for apoE3), or as having a sequence that has at least 90% sequence identity to the particular sequence defined in present independent claims 30 and 83, which sequence is relative to SEQ ID NO: 2. All of the independent claims, claims 30 and 79-83, require that the encoded polypeptide lack amino acids 260-299 of SEQ ID NO: 2.

Applicants discovered that the carboxyl-terminal region, i.e., amino acids 260-299, of apoE polypeptides is responsible for promoting hypertriglyceridemia. Applicants used a series of

apoE deletion mutants extending from amino acid 1 to amino acids 185, 202, 229 and 259 to map the region responsible for the hypertriglyceridemic effect. By expressing an apoE polypeptide lacking amino acids 260-299, Applicants identified an apoE polypeptide capable of promoting cholesterol-lowering without inducing hypertriglyceridemia (see, e.g., page 16, lines 23-27, of the specification).

Applicants, who are research scientists, have continued to dissect the mechanism by which amino acids 260-299 of apoE polypeptides promote hypertriglyceridemia. In a post-filing date publication, Applicants indicated that “[t]he identification of amino acid residues within the carboxyl-terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research” (see p. 19786, col. 2, 2<sup>nd</sup> ¶, of Kypreos et al., *J. Biol. Chem.* 276:19778-19786, 2001). The Examiner points to this statement as evidence that, at the time of filing of the present application, Applicants did not possess a genus of nucleic acids that express a secreted polypeptide which, when expressed in a mammal, lowers serum cholesterol without inducing hypertriglyceridemia. Applicants respectfully disagree with the Examiner’s interpretation. This statement merely indicates that, as of April 2001, Applicants had not yet identified the specific amino acids **within the carboxyl-terminal tail of apoE** (i.e., amino acids 260-299) responsible for causing hypertriglyceridemia; it does not suggest that Applicants did not possess (or sufficiently describe) the recited genus of apoE-encoding nucleic acids.<sup>1</sup> In any event, the region that includes amino acids 260-299 of apoE, which is described by Applicants as being responsible for causing hypertriglyceridemia, are specifically **excluded** from the polypeptides encoded by the nucleic acid molecules recited in present independent claims 30 and

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<sup>1</sup> The specific amino acids within the carboxyl-terminal region of apoE (i.e., a.a. 260-299) were later identified by

79-83, and claims dependent therefrom. By excluding the region containing these amino acids from the polypeptide encoded by the recited nucleic acid molecule, Applicants have achieved an apoE polypeptide that retains the ability to lower cholesterol without also inducing hypercholesterolemia.

### *The Written Description Requirement: The Legal Standard*

The written description requirement, as set forth in 35 U.S.C. § 112, first paragraph, requires that the “specification shall contain a written description of the invention.” The M.P.E.P. § 2163 states:

The written description requirement has several policy objectives. “[T]he ‘essential goal’ of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed.” *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

Furthermore, “[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention” (M.P.E.P. § 2163).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including *description of an actual reduction to practice*, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, *or by describing distinguishing identifying characteristics sufficient to show that the*

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Applicants; this subject matter is disclosed in copending Application No. 11/220,485.

*applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by “whatever characteristics sufficiently distinguish it”). (M.P.E.P. § 2163; emphasis added.)

#### *Applicants have Satisfied the Written Description Requirement*

As is discussed above, present claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89 are directed to a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia by administering a replication-defective adenoviral vector containing a nucleic acid encoding, *inter alia*, a secreted apoE polypeptide lacking amino acids 260-299 of SEQ ID NO: 2. For the purposes of written description, all that is required is that Applicants’ specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2163; *Regents of the University of California v. Eli Lilly & Co.*, *supra*). Applicants can demonstrate possession by providing an actual reduction to practice of the claimed invention (see, e.g., *Pfaff v. Wells Elecs., Inc.*, *supra*; *Regents of the University of California v. Eli Lilly & Co.*, *supra*; and *Amgen, Inc. v. Chugai Pharmaceutical*, *supra*), or by describing the invention with all of its limitations using a description that clearly conveys the claimed invention (*Lockwood v. American Airlines, Inc.*, *supra*). “The description need only describe in detail that which is new or not conventional.” (*Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, at 1384, 231 USPQ 81, at 94 (Fed. Cir. 1986)). Applicants have clearly satisfied all of these requirements.

*Applicants' Specification Describes Actual Reduction to Practice*

Applicants clearly demonstrate possession of the claimed apoE polypeptides by presentation of several examples of a reduction to practice of the invention.

On page 29, line 21, through page 32, line 23, of the specification, Applicants describe assessing the effects of truncated apoE polypeptides that lack at least the carboxy-terminal amino acids 260-299 of full-length wild-type apoE. Applicants infected apoE-deficient mice with recombinant adenoviruses encoding one of several apoE polypeptides, specifically an apoE polypeptide lacking amino acids 186-299, amino acids 203-299, amino acids 230-299, or amino acids 260-299 of full length wild-type apoE. Expression of each of these truncated apoE polypeptides resulted in a reduction in serum cholesterol levels without an increase in triglyceride levels. These examples clearly demonstrate that Applicants had reduced several different embodiments of the invention to practice as of the filing date of the present application, and unequivocally demonstrate that Applicants were in possession of the claimed invention. For this reason, present claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89 satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

In addition, possession of a claimed invention can also be demonstrated by describing the claimed invention using “relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus” (M.P.E.P. § 2163) Applicants have clearly satisfied this requirement, as is clear from the description above of Applicants' reduction to practice of the presently claimed method. Present

claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89 require not only the expression of particular amino acids, relative to SEQ ID NO: 2, but also biological activity (i.e., the ability to lower serum cholesterol levels without inducing hypertriglyceridemia). These distinguishing identifying characteristics are more than sufficient to show that the Applicants were in possession of the claimed invention as of the filing date (*see Pfaff v. Wells Elecs., Inc., supra*).

In sum, there can be no question that Applicants were in possession of the claimed genus of ApoE-encoding nucleic acids at the time the application was filed, and that one skilled in the art would recognize Applicants' disclosure as a description of the invention defined by present claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89. Applicants have clearly demonstrated possession of the claimed Apo-E encoding nucleic acids and their use in the recited methods by describing the Apo-E encoding nucleic acids with all of their limitations and by showing reduction to practice of the Apo-E encoding nucleic acids, as is required (see M.P.E.P. § 2163, *supra*). As a result, Applicants' specification clearly satisfies the written description requirement, as set forth by the case law and the M.P.E.P., and Applicant requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 30, 33-34, 36, 43-44, 47, 53-55, 57, 59, 61-62, and 72.

#### *Enablement*

Claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-62, and 64-72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the specification is only enabling for:

a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprises [sic: comprising]

intravascularly administering to said mammal a replication defective adenoviral vector encoding a secreted polypeptide consists [sic: consisting] of residues 1-185, 1-202, 1-229, or 1-259 of any one of SEQ ID Nos. 14-19, with SEQ ID NO: 15 as the elected species, when expressed and secreted in said mammal, lowers the total serum cholesterol without inducing hypertriglyceridemia. (Office Action, pp. 6-7.)

The Examiner suggests that the specification is not enabling for “a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia by intravascularly administering to said mammal other recombinant replication-defective adenoviral vector as broadly claimed” (Office Action, p. 7; emphasis in original). For the following reasons, Applicants respectfully disagree.

A specification is presumed to be in compliance with the enablement requirement of 112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the Applicants’ disclosure coupled with information known in the art *without undue experimentation*. For the Office to sustain a rejection on the grounds of enablement, it must provide *evidence* that the claimed method could not be performed without undue experimentation.

The Examiner admits that the specification enables a method of lowering cholesterol in a mammal expressing a functional LDL receptor without causing hypertriglyceridemia by using vectors encoding secreted ApoE polypeptides having residues 1-185, 1-202, 1-229, or 1-259 of any one of SEQ ID Nos. 14-19. Accordingly, the sole issue is whether the specification enables the use of vectors encoding ApoE polypeptides other than these specific ApoE-encoding vectors. Applicants submit that it does.

A review of the Examiner's analysis in support of the rejection reveals that his conclusion is based on two principle misgivings. The first concerns the field of gene therapy generally, while the second is more specific to the claimed invention as it concerns the role of ApoE in combination with gene transfer techniques.

#### Applicants' Gene Therapy Methods are Fully Enabled

The Examiner cites several references in support of his assertion that, "[a]t the effective filing date of the present application (4/6/2000),...gene therapy...was and still remains unpredictable with respect to the attainment of desired therapeutic effects...the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (Office Action, p. 9; emphasis in original). Thus, it appears that the Examiner's position is that the field of gene therapy, generally, will not be enabled so long as it remains "immature" and "not routine" (Office Action, p. 10). This position does not reflect the applicable legal standard.

The proper standard for compliance with enablement is not absolute predictability but *objective enablement* - would one reasonably skilled in the art be able to make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation? Evidence provided by Applicants need not be conclusive but merely convincing to one of skill in the art (see, e.g., M.P.E.P. § 2164.05). In this case, Applicants submit that the compelling animal data provided in the Zannis Declaration filed on February 23, 2006, is sufficiently "convincing" that one of ordinary skill in the art would not doubt its feasibility or its application to mammals other than mice. Moreover, the *in vivo* successes documented in the instant specification (see, particularly, pages 29-36) clearly

outweigh any speculative allegations of unpredictability set forth in the prior art.

In *In re Brana*, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), the court cautioned against confusing “the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption,” citing *Scott v. Finney*, 34 F3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). The rejection before the court for review in *Brana* was for lack of enablement under the first paragraph of 35 U.S.C. § 112 (although the court discussed the issues raised in the appeal in the context of both enablement and the utility requirement of 35 U.S.C. § 101):

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. [ ] Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. [ ]

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. [ ] Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *Brana*, 51 F3d at 1568, 34 USPQ2d at 1442-43 (citations omitted).

While the claims involved in *Brana* were directed to chemical compounds taught to be useful in treating cancer, Applicants submit that these principles can be applied to the present claims directed to methods of gene therapy using vectors encoding ApoE polypeptides, especially in

light of the Examiner's apparent position that gene therapy in general is non-enabled. Thus, as in *Brana*, where the Court held that the applicants' declaratory evidence showing antitumor activity in an *in vivo* mouse model was sufficient to satisfy the utility and enablement requirements of 35 U.S.C. § 112, first paragraph, Applicants submit that the case law compels the Examiner to conclude that Applicants' declaratory evidence, which unequivocally demonstrates that several vectors encoding truncated ApoE polypeptides, when administered to an ApoE-deficient mouse having a functional LDL receptor, are capable of reducing cholesterol without inducing hypertriglyceridemia, should also be deemed sufficient evidence demonstrating that the methods of present claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Indeed, the Examiner acknowledges that the specification enables a method of using a replication defective adenoviral vector encoding a secreted polypeptide having residues 1-185, 1-202, 1-229, or 1-259 (SEQ ID NOs. 14-19; see Office Action, pp. 6-7). Thus, Applicants cannot understand how the Examiner can reconcile his conclusion that the use of these ApoE-encoding vectors for gene therapy are enabled, while also holding that Applicants have not enabled methods for using adenoviral vectors in gene therapy in general. As noted above, for the Office to sustain a rejection on the grounds of enablement, the Office must provide evidence that the claimed method could not be performed without undue experimentation. On the central issue of unpredictability in the art, Applicants note that the majority of the "evidence" cited by the Examiner is either out of date, not pertinent to the claimed invention, or both. Certainly, the cited prior art fails to rebut Applicants' evidence that the method of present claims 30, 34, 36, 43, 44, 47, 51, 53, 56, 58, 60-62, 72, and 79-89 are enabled to their full breadth. Accordingly, on the issue of the enablement of Applicants' gene

therapy methods in general, Applicants submit that the disparity in the Examiner's conclusions should be resolved in Applicants favor.

Applicants have Enabled ApoE-Encoded Adenoviral Vectors as Broadly Claimed

The Examiner's second principle misgiving is his conclusion that the specification does not enable the full breadth of recombinant adenoviral vectors encoding ApoE polypeptides as recited in present independent claim 30 and claims dependent therefrom. As is discussed above, the test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the Applicants' disclosure coupled with information known in the art *without undue experimentation*. For the Office to sustain a rejection on the grounds of enablement, it must provide *evidence* that the claimed method could not be performed without undue experimentation. Applicants agree that the identification of polypeptides having at least 90% sequence identity to SEQ ID NO: 2 (i.e., ApoE3), but lacking amino acids 260-299 of SEQ ID NO: 2, and the ability to reduce cholesterol without inducing hypertriglyceridemia when administered to a mammal in an adenoviral vector would require some experimentation; just as clearly, the experimentation is not "undue." It is well established that the fact that some experimentation may be required to practice the invention is not justification for rejecting a claim for lack of enablement. In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987), the requirement that antibodies be tested for binding to an antigen was held not to support a lack of enablement rejection; experimentation admittedly was required, but it was routine, not undue.

The present situation is, in all important aspects, indistinguishable from the facts in *In re*

*Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), in which the Federal Circuit held that the applicant's claim was enabled, despite the necessity for screening to obtain antibodies, because the process of antibody screening was straightforward. It follows that the present claims are also enabled, even if some screening would be necessary to identify ApoE polypeptides satisfying all of the limitations of present independent claim 30 and claims dependent therefrom. Given the breadth of Applicants' disclosure, the amount of guidance presented in Applicants' specification, the presence of working examples, and the level of skill in the art, the identification of desirable ApoE polypeptides requires no more than routine methods and does not constitute undue experimentation. Thus, the present claims are enabled, even if some screening would be necessary to identify the particular ApoE polypeptides needed to give the desired cholesterol-lowering effect without inducing hypertriglyceridemia. The proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). Applicants have clearly met this standard. Accordingly, the rejection of independent claim 30, and claims dependent therefrom, under U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn and should not be applied to new claims 79-89.

Thus, for the reasons given above, we submit that the scope of the present claims invention is commensurate with the instant specification's scope of enablement. Accordingly, Applicants request reconsideration and withdrawal of the enablement rejection in view of the amendments to the claims and the remarks herein.

### Provisional Obviousness-Type Double-Patenting Rejection

Claims 30, 33-34, 43-44, and 47 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 37, 39-40, and 42-58 of copending Application No. 11/220,485. When the pending claims are found to be otherwise allowable except for this ground of rejection, Applicants will address the rejection, including consideration of whether to file a terminal disclaimer.


CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including December 28, 2006.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 12 December 2006

  
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For Paul T. Clark  
Reg. No. 30,162

TOOD ARMSTRONG, Ph.D.  
Reg. No. 54,590

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045